REMARKS

STATUS OF CLAIMS

Previously withdrawn Claims 5-21 have been canceled. In addition, Claims 26, 30, 32, and 33 have been canceled. Claims 22 and 24 have been amended. Lastly, new Claims 34-38 have been added. Consequently, Claims 1, 3, 4, 22, 24, 25, 27-29, 31 and 34-38 are pending. Support for these claim amendments and new claims can be found throughout the specification and in the originally filed claims. For example, support for new Claims 34-38 can be found in originally filed Claim 3 part (b). No new matter has been added.

REJECTIONS UNDER 35 U.S.C. § 112, first paragraph

Claims 1, 3, 4, and 24-25 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement. The Examiner notes that the specification is "enabling for a method of impairing movement of a CLA+ memory T cell within or to the skin of a mammal, said method comprising *locally, topically, intradermally, or transdermally administering* to said mammal an effective amount of an antibody against CTACK, whereby administration of said antibody impairs movement of a cutaneous lymphocyte-associated antigen (CLA)+ memory T cell within or to the skin of said mammal." But the Examiner alleges that the specification is not enabling for *systemic administration* of an antibody against CTACK.

> **Claim 1** (from which Claims 3, 4, 24, 25 and 34-38 depend) reads as follows:
> A method for impairing movement of a cutaneous lymphocyte-associated antigen$^+$ (CLA$^+$) memory T-cell within or to the skin of a mammal, said method comprising administering to said mammal an effective amount of an antibody against cutaneous-T-cell-attracting chemokine (CTACK), whereby administration of said antibody impairs movement of said cutaneous lymphocyte-associated antigen$^+$ memory T-cell within or to the skin of said mammal.
>
> **Claim 3** reads as follows:
> The method of Claim 1, wherein said movement is within said skin.
>
> **Claim 4** reads as follows:
> The method of Claim 1, wherein said antibody neutralizes cutaneous-T-cell-attracting chemokine.

Amended Claim 24 reads as follows:
The method of Claim 1, wherein said administering is local.

Claim 25 reads as follows:
The method of Claim 1, wherein said cutaneous lymphocyte-associated antigen$^+$ memory T-cell moves into the dermis or epidermis of said skin.

Notably, the subject-matter of new Claims 34-38 was previously present in Claim 24.

New Claim 34 reads as follows:
The method of Claim 1, wherein said administering is systemic.

New Claim 35 reads as follows:
The method of Claim 1, wherein said administering is topical.

New Claim 36 reads as follows:
The method of Claim 1, wherein said administering is subcutaneous.

New Claim 37 reads as follows:
The method of Claim 1, wherein said administering is intradermal.

New Claim 38 reads as follows:
The method of Claim 1, wherein said administering is transdermal.

Applicants note that contrary to the Examiner's allegation, the specification describes suppression of skin inflammation by *systemic administration* of an antibody against CTACK. Specifically, mice sensitized to di-nitrofluorobenzene (DNFB) received intraperitoneal injections of neutralizing antibodies against mCTACK. See, for example, page 78, lines 24-27. *It is general knowledge that matter injected into the intraperitoneal cavity is taken up systemically.* Here, two hours after the second intraperitoneal injection, the mice were challenged with DNFB on their ear. See, for example, page 78, lines 27-30. Monitoring of DNFB challenge-induced ear swelling (24-72 hours) confirmed significant suppression of skin inflammation in anti-mCTACK-treated mice when compared to mice injected with an isotype control ($p>0.01$). See, for example, page 80, lines 16-18. Furthermore, additional experiments revealed that anti-

mCTACK treatment provided superior inhibition of contact allergen-induced skin inflammation compared to pre-treatments with the topical immunosuppressant tacrolimus/FK506 (1%). Notably, topical tacrolimus treatment shows strong clinical efficacy in patients suffering from atopic dermatitis. See, for example, page 80, lines 20-24.

It should be noted that distribution analysis described in the specification on page 65, line 5 to page 68, line 24 show that *CTACK is extremely tissue specific*. See, for example, page 66, lines 26-27. In fact, CTACK is not only highly tissue-specific, but its selective expression in the skin is restricted to the epidermis. See, for example, page 67, lines 9-11. CTACK message is detected in keratinocytes, the predominant cell type in the epidermis. See, for example, page 67, lines 21-22. Most abundant expression of CTACK was observed in keratinocytes of the basal layers of the epidermis. Upon normal differentiation keratinocytes of suprabasal layers appear to produce lower amounts of CTACK protein. See, for example, page 68, lines 7-9. As CTACK expression is skin-specific, systemic administration of an antibody against CTACK *targets skin specifically*. The suppression of skin inflammation by *systemic administration* of an antibody against CTACK was specifically described in the specification and therefore enables one of skill in the art to practice the claimed invention.

In light of the above arguments, claims 1, 3, 4, 24, 25, and 34-38 are believed to be enabled by the specification. As such, Applicants respectfully request withdrawal of this rejection under 35 U.S.C. § 112, first paragraph.

Claims 22 and 26-33 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement. The Examiner notes that the specification is "enabling for a method of treating a patient suffering from *contact allergen-induced skin inflammation* or *allergic contact dermatitis* comprising administering an effective amount of an antibody against cutaneous-T-cell attracting chemokine (CTACK)." But the Examiner alleges that the specification is not enabling for a method of treating a patient suffering from a *skin disorder* comprising administering an effective amount of an antibody against CTACK.

As noted above, Claims 26, 30, 32 and 33 have been canceled. The remarks below address the present rejection as it pertains to the subject matter of pending Claims 22 and 27-29.

> **Amended Claim 22** (from which Claims 27-29 and 31 depend) reads as follows:
> A method for treating a patient suffering from a skin disorder selected from the group consisting of allergic-contact dermatitis, psoriasis, wound healing, and carcinoma comprising administering an effective amount of an antibody against cutaneous-T-cell-attracting chemokine.
>
> **Claim 27** reads as follows:
> The method of Claim 22, wherein said skin disorder is allergic-contact dermatitis.
>
> **Claim 28** reads as follows:
> The method of Claim 22, wherein said skin disorder is psoriasis.
>
> **Claim 29** reads as follows:
> The method of Claim 22, wherein said skin disorder is wound healing,
>
> **Claim 31** reads as follows:
> The method of Claim 22, wherein said skin disorder is carcinoma.

CTACK is specifically expressed in skin and selectively chemoattracts CLA+ skin-homing T cells. See, for example, page 70, lines 11-13. The CLA+ memory T cell subset constitutes a skin-associated population of memory cells that preferentially extravasate at normal and chronically inflamed cutaneous sites. This subpopulation has been shown to be involved in local immunity and inflammatory cutaneous reactions. See, for example, page 69, lines 23-28.

The specification describes the treatment of a skin disorder selected from the group consisting of allergic-contact dermatitis, psoriasis, wound healing, and carcinoma by administering an antibody against CTACK. Distribution analysis described in the specification on page 65, line 5 to page 68, line 24 show that CTACK RNA is expressed by human keratinocytes and upregulated by pro-inflammatory cytokines. See, for example, page 65, lines 29-30. Furthermore, CTACK expression was shown to be suppressed after treatment with clobetasol propionate, a known therapeutic for inflammatory or autoimmune skin disease. Notably, the skin disorders claimed

all involve an inflammatory infiltration of cells from blood into skin. In these skin disorders, blocking the inflammatory infiltrate would be therapeutic as it would reduce inflammation associated with these disorders.

Appendix A contains publication abstracts that support a nexus between CTACK and allergic-contact dermatitis, psoriasis, wound healing, and carcinoma.

- Kakinuma *et al.*, "Increased serum cutaneous T cell-attracting chemokine (CCL27) levels in patients with atopic dermatitis and psoriasis vulgaris," *J Allergy Clin Immunol*, **111(3)**:592-597 (2003).
  Results suggest that CTACK might be one of the important chemokines for the pathogenesis of **atopic dermatits** and **psoriasis** vulgaris.

- Homey *et al.*, "CCL27-CCR10 interactions regulate T cell-mediated skin inflammation," *Nat Med*, **8(2)**:117-118 (2002).
  Findings indicate that CCL27-CCR10 interactions have a pivotal role in T cell-mediated **skin inflammation**.

- Szpaderska *et al.*, "Differential injury responses in oral mucosal and cutaneous wounds," *J Dent Res*, **82(8)**:621-626 (2003).
  Findings demonstrate that diminished inflammation is a key feature of the privileged repair of oral mucosa as compared to a cutaneous **wound**.

- Müller *et al.*, "CCR10 expression by malignant melanoma cells: implications for tumor growth and metastasis," Abstract for Investigative Dermatology 2003 Meeting, Fontainbleau Hilton, Miami Beach, Florida, April 30-May 4, 2003.
  In vivo, neutralization of mCCL27 (mCTACK) resulted in delayed primary tumor growth of human **melanoma** cells in a SCID mouse model.

Appendix B contains data that provides additional evidence of a nexus between CTACK and a carcinoma as well as the therapeutic effect of an antibody against CTACK on a carcinoma *in vivo*.

CTACK was shown to induce both migration and proliferation of melanoma cells. In addition, blocking CTACK with an anti-mCCL27 (mCTACK) antibody was found to impair primary **melanoma** growth in mouse previously injected with tumor cells (either LOX or MV3).

In light of the above amendments and arguments, Claims 22, 27-29, and 31 are believed to be enabled by the specification. As such, Applicants respectfully request withdrawal of this rejection under 35 U.S.C. § 112, first paragraph.

CONCLUSION

It is believed that the foregoing amendments and arguments place this application now in condition for allowance. Therefore, favorable action allowing pending claims 1, 3, 4, 22, 24, 25, 27-29, 31, and 34-38 is respectfully solicited.

Respectfully submitted,

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